

# QUEENS COLLEGE

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January 12, 1973

Dr. Frederic W. Nordsiek  
Associate Scientific Director  
The Council for Tobacco Research -  
U.S.A., Inc.  
110 East 59th Street  
New York, New York 10022

Dear Dr. Nordsiek:

I have received your letter of January 10 and the enclosed grant application submitted to C.T.R. by Professor Luigi Valzelli. I have read the grant application very carefully and will try to provide some comments which may be useful to you in its evaluation.

The general objective of this proposal is one which I believe to be highly meritorious inasmuch as it encompasses a very important and often neglected series of variables that appear more and more to be highly relevant to both pharmacology as well as to physiological mechanisms underlying behavior. The basic model which Professor Valzelli describes is one which he has had extensive experience in developing, and his previous research on the "isolation syndrome" has suggested that principles of biochemical pharmacology are highly relevant to this model in that it represents one means by which presumed mechanisms underlying centrally-acting drugs may be investigated. The interrelationship between behavioral, pharmacological, and biochemical parameters affected by nicotine appears to me to be a not only useful but very important area for investigation. Having at his disposal a well-studied and quantifiable measure, such as aggressive behavior, enables Professor Valzelli to systematically carry out the objectives which he has specified.

Differences in the effect of nicotine and the potential relationship between differences in action based upon environmentally conferred biochemical differences in animals and their relationship in man is an exciting notion which does seem to deserve attention. In going through each of the eight areas within which Professor Valzelli has proposed examining the effects of nicotine, generally with regard to differences based upon variables related to differential housing, each appears to be a logical succession of experiments leading to some very interesting areas of investigation. Those which appear

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January 12, 1973

particularly interesting and which, to my knowledge, have certainly not been dealt with previously concern differences between the active levels of nicotine and their presumed relationship to normal and aggressive behavior. The effects of nicotine upon aggressive behavior are, of course, in themselves highly interesting in that the central effects of compounds, particularly alkaloids, which have in laboratory investigation been shown to alter aggressive behavior also usually involve changes not only in the biogenic amines, but also several other important substrates of brain metabolism. This is particularly important in the case of several of the benzodiazepines, which have been shown to alter the aggressive behavior induced by a variety of experimental techniques. Professor Valzelli's work in this area also is well-known, and I think it is particularly appropriate that he has indicated a consideration of brain N-acetyl-aspartic acid levels since these are apparently altered in animals in which experimentally-induced aggressive behavior has been manifested and such alterations are modified by anti-aggressive drugs.

A final aspect of this proposal which I think deserves some comment is the suggestion that the central effects of nicotine be considered in the partial absence of contributory aminergic nerve endings and that this paradigm be combined for aggressive and non-aggressive rats. I believe that, experimentally, this would represent a unique approach to the specification of biochemical contributions to both the effect of nicotine as well as the interaction of nicotine with those mechanisms responsible for the mediation of aggressive behavior. Personally, I like this approach very much and believe that it fits in very consistently with current methodology in neuropharmacology.

I have no question whatsoever as to the adequacy or validity of the procedures that Professor Valzelli has outlined to carry out this work. I think certainly that his well-known publications in this area and the practiced use of these techniques as have been indicated in his prior publications speak most favorably for both his competence as a scientist and his ability to carry out the proposed research.

In general, my appraisal of this proposal leads me to a highly favorable opinion of both the scientific merit as well as the importance of those contributions that could result from the proposed experiments. I believe that it certainly deserves a high level of priority.

I hope that these comments are useful to you; and if you believe that any of the other materials relevant to this proposal mentioned in

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Dr. Frederic W. Nordsiek

-3-

January 12, 1973

your letter may be helpful in further evaluation, I shall be very pleased to look at these as well.

Thank you for giving me the opportunity to read and evaluate this proposal.

With best wishes,

Sincerely,

*Walter B. Essman/ss*

Walter B. Essman, M.D., Ph.D.  
Professor

WBE:ss

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